

## **REMARKS/ARGUMENTS**

Claims 44-107 are pending in this application. The elected Group III claims (nos. 46, 52, 53, 59, 65, 70 and 90) are rejected. The non-elected claims, nos. 44, 45, 47-51, 54-58, 60-64, 66-69, 71-89 and 91-107, have been withdrawn by the Examiner from further consideration in this application.

Claim 46, which is the only independent claim among those which are rejected, is amended in this Response to particularly recite that the claimed method is directed to diabetic wound healing. Support for the amendment to claim 46 is found at several locations in the specification of the application as filed, most specifically at from p. 25, line 14 to p. 26, last line. Thus there is no issue of new matter raised by the claim amendment. Entry of the amended claims into the file of the present application is respectfully solicited.

Provided with this Response is a "Third Declaration of Prof. Dr. Hermann Haller Under 37 C.F.R. §1.132". The declaration provides additional evidence (i.e., to that contained in Haller I and Haller II) which supports the Novelty and Non-Obviousness of applicants' (amended) claims presently under examination. The Examiner is respectfully requested to enter and consider the declaration, as well as to reconsider and withdraw all of the rejections of claims 46, 52, 53, 59, 65, 70 and 90 in light of the evidence provided, in conjunction with the attorney remarks provided in this Amendment.

Applicants note with appreciation the Examiner's statement on p. 2 of the Office Action that the rejection under 35 U.S.C. §103 set forth in the Office Action mailed June 23, 2008 is withdrawn.

### **Rejection Under 35 U.S.C. §102**

Claims 46, 52, 53 and 90 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Smith-Swintosky, et al. Published US Patent Application No. 2003/0130197 ("the '197 reference"). The rejection is respectfully traversed.

In response to the rejection, claim 46 has been amended such that the subject claim now recites a method for diabetic wound healing through administration of a weekly dosis of 1 to 90

International Units (IU) EPO/kg body weight to a subject in need of such treatment, in order to achieve in the case of said subject a desired amount of diabetic wound healing.

The '197 reference is not believed by applicants to be relevant to the method as now claimed. That is, the reference relates to neuro-protective peptides and discloses on p. 12 in Example 5 an EPO treatment against ischemic injury. However, as noted above, claim 46 is now amended so as to recite a method for treatment of a diabetic wound. This feature is thus now also shared by the remaining rejected claims that depend from claim 46. As pointed out by the Examiner, i.e., at p. 3 of the Office Action, a three-day treatment with 1.32 IU EPO per day per rat is disclosed by the Smith-Swintosky, et al. reference, wherein the rats have a body weight of 250-300 grams. The treatment thus described was for the purpose of, as indicated above, analyzing the effect of EPO on injuries causing cerebral ischemia. This is clearly not the same as treating diabetic wounds. Moreover, further according to the Smith-Swintosky, et al. reference, the treatment did not produce any therapeutic effect in the rats - see, e.g., paragraph [0142] on p. 12 of the reference and accompanying figures 19 and 20. It is only at higher dosages, which fall outside of the dosage recited in applicants' claims, that the treatment has a beneficial effect.

As indicated above, provided with this Amendment is a third declaration of Prof. Dr. Haller under 37 C.F.R. §1.132. Dr. Haller's declaration discusses in great detail the molecular and cellular differences between wound healing in diabetes and mechanisms of injury and regeneration following ischemic trauma. This declaration, then, provides additional significant evidentiary support of applicants' contention that the disclosure in the '197 reference with regard to the treatment of ischemic injury in rats is irrelevant to and certainly does not teach or suggest the method as now recited in applicants' pending claims under examination.

In summary, therefore, while it may be said that the reference does disclose the administration of EPO within the dosage range recited in applicants' claims, the purpose of such administration is to determine whether such dosis would counter the effects of cerebral ischemia, and not for the purpose of healing diabetic wounds as recited in applicants' pending claims. Moreover, as also indicated above, no beneficial effect was encountered, in the treatment of ischemia, when the EPO was administered within applicants' claimed dosage range. That is, the

authors of the reference were required to utilize dosages higher than those claimed, while no amount of EPO was shown to heal diabetic wounds.

Based on the remarks provided above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 U.S.C. §102(e) of applicants' claims 46, 52, 53 and 90.

### **Rejection Under 35 U.S.C. §103**

At p. 5 of the Office Action claims 46, 52, 53, 59, 65, 70 and 90 are rejected under 35 U.S.C. §103 over Smith-Swintosky, et al. US 2003/0130197 (i.e., the 'primary' reference) in view of Krussel, JS, et al.; Janquet, Kai, et al.; Amgen, Inc. EP 0 613 683; USP 6,274,158 of Zaharia Czeizler and USP 6,748,154 of Westenfelder (the 'secondary' references). This rejection is, also, respectfully traversed.

As previously noted, applicants have amended independent claim no. 46, which is the only independent claim of those that are rejected, such that the subject claim now recites a method for diabetic wound healing involving the administration of low dosis EPO in an amount unexpectedly found to be useful in producing a desired amount of healing of such diabetic wounds. As pointed out above in the discussion relating to the rejection under 35 U.S.C. 102(e), while the reference does disclose the administration of EPO within the dosage range recited in applicants' claims, the purpose of such administration is to determine whether such dosis would counter the effects of cerebral ischemia, and not for the purpose of healing diabetic wounds as recited in applicants' pending claims. The significant differences in the mechanism of ischemia treatment, versus that involved in the treatment of diabetic wounds are clearly set forth in the "Third Declaration of Prof. Dr. Hermann Haller Under 37 C.F.R. §1.132" that is being filed with this Amendment. In addition, no beneficial effect was encountered, even with regard to the treatment of ischemia (much less in the treatment of diabetic wounds - as claimed by applicants), when the EPO was administered within applicants' claimed dosage range. The authors of the reference were required to utilize dosages higher than those claimed to obtain beneficial results in the ischemia treatment, while no amount of EPO was shown to heal diabetic wounds. Based on the reasons given, therefore, the method as recited in applicants' presently amended claims is

clearly distinguishable from the disclosure of the Smith-Swintosky, et al. reference in that the reference neither teaches, nor even suggests, applicants' claimed method.

Applicants recognize, of course that the rejection is based, not on Smith Swintosky, et al. alone, but on the combination of that reference with several additional references. Moreover, applicants are well aware that a 'combination' rejection of the type made herein is not overcome by attacking, individually, each of the references cited in the combination. Applicants submit, however, that as developed further below, the cited 'secondary' references are included in the combination by the Examiner due to their disclosure of matters, such as those disclosed at the top of p. 6 of the Action, i.e., relating to oral or pulmonary administration of EPO and the inclusion of an additional ingredient which stimulates endothelial progenitor cells. The added disclosure of these secondary references, however, does not supply the element(s) of the presently claimed invention which are entirely missing from the disclosure contained in Smith-Swintosky, et al., i.e., the concept of healing diabetic wounds via the administration to a subject in need thereof of a pharmaceutical composition comprising subpolycythemic erythropoietin doses corresponding to a weekly dose of 1 to 90 IU EPO/kg of body weight. As such, applicants contend that even the combination of some or all of the secondary references with the 'primary' Smith-Swintosky, et al. reference does not serve to teach or even suggest applicants' method as now claimed.

As can be seen from the discussion contained on pp. 6-7 of the Office Action, the Westenfelder reference is cited due to its disclosure of what comprises a subpolycythemic dosis of erythropoietin in that such dosages do not induce polycythemia. Further according to the Action, Zaharia Czeizler is cited due to its teaching regarding the oral, subcutaneous and intravenous administration of EPO for the treatment of bleeding due to surgical treatments (i.e., wounds made by a surgical process - not diabetic wounds). Amgen EP 0 613 683 is cited for its teaching that EPO may be formulated for inhalers. Further according to the Office Action (see p. 6) the Krussel J.S., et al. reference is cited due to its teaching that the compound VEGF (i.e., vascular endothelial growth factor) stimulates endothelial progenitor cells and induces angiogenesis. Finally, p. 7 of the Office Action indicates that Janquet, Kai, et al. is cited for a teaching that EPO and VEGF exhibit equal and angiogenic potential and that VEGF has been shown to enhance angiogenesis in ischemic diseases.

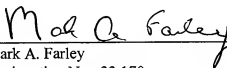
However, even the combination of the disclosure of the secondary references with that of Smith -Swintosky, et al. would neither teach nor suggest applicants' method as now recited in the claims under examination - due at least in part to the elements of the presently claimed invention missing from Smith-Swintosky et al. (see the discussion above). Thus, neither Smith-Swintosky, et al. by itself, or in combination with one or more of the secondary references, teaches or even suggests applicants' claimed method. The Examiner, therefore, is respectfully requested to reconsider and withdraw the rejection of applicants' claims under 35 U.S.C. §103.

### Summary

Applicants respectfully submit that in view of the amendment of claim 46, taken in conjunction with the evidence contained in the third 1.132 declaration of Prof. Dr. Haller submitted herewith and the attorney remarks provided above, the claims under examination are entirely distinguished over the cited prior art, whether taken individually or in combination. The Examiner is, therefore, requested to reconsider and withdraw all of the pending rejections of applicants' claims and to issue a Notice of Allowance for this case. If the Examiner does not agree and believes that an interview would advance the progress of the application, he is invited to telephone applicants' representative at the number below so that such an interview may be arranged.

Respectfully submitted,

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